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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KAUSHAL, SUMESH	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/255,963	Applicant(s) MA, PETER X.	
	Examiner Sumesh Kaushal	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,22-38 and 40-47* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,22-38 and 40-47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/03/01 has been entered.

Claims 45-47 were newly filed.
Claim 39 was canceled.
Claims 1, 11, 23, 34, 40 and 41 were amended.
Claims 1-20, 22-38 and 40-47 were pending and were examined in this office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The references cited herein are of record in a prior Office action.

If the claims are amended, added and/or canceled in response to this office action the applicants are required to follow Amendment Practice under 37 CFR § 1.121 (http://www.uspto.gov) and A CLEAN COPY OF ALL PENDING CLAIMS IS REQUESTED.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-38 and 40-47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of making a Calcium-GDL-alginate hydrogel system wherein the shrinking, swelling or maintaining of the hydrogel system is selectively controlled by varying a calcium ion concentration of a medium into which the three dimensional cross-linked hydrogel system is introduced after corss-linking, does not reasonably provide enablement for any and all three-dimensional cross-linked hydrogel systems wherein the any and all hydrophilic polymers are cross-linked using any and all cation-releasing compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

The instant claims are drawn to a method for preparing a three-dimentional hydrogel system and a composition to make the same comprising adding a cation-relasing compound to a mixture of at least one hydrophilic polymer and source of cations to provide a three dimensional crosslinked hydrogel system and selectively controlling shrinkage, swelling or maintaining of the hydrogel system by varying cation concentration of a medium into which the hydrogel system is introduced, wherein the cation in the medium is selected to be the same cation as the cation in the hydrogel system.

The specification teaches the preparation of LH alginate gels prepared with $CaCO_3$-GDL (page 13, table-1). The specification further teaches the effects of calcium concentration on gel homogeneity, syneresis (volume ratio of gel to the suspension before gelation), mechanical properties and swelling ratio in tissue culture (spec. pages 14-16). In addition the specification

teaches incorporation of MC3T3-E1 osteoblast cells into LH alginate gels, wherein the calcium ion concentration was adjusted to 0.0030M to control the gel size (spec. page 16).

However, the instant specification fails to disclose a single working example to make a three-dimensional cross-linked system wherein the any and all hydrophilic polymers are cross-linked using any and all cation-releasing compounds. At best the specification only provides enablement for Calcium–GDL-alginate hydrogel system wherein the shrinking, swelling or maintaining of the hydrogel system is selectively controlled by varying a calcium ion concentration of a medium into which the three-dimensional cross-linked hydrogel system is introduced after cross-linking.

The state of the art at the time of filing teaches that alginate is a polysaccharide obatained from marine algae, which comprises mannuronate diad (MM), guluronate diad (GG) and hetro diad (GM). The GG-diad has higher selectivity for Ca2+ than MM or GM-diads due to the differences of the chain conformations in these blocks. In addition, the presence of simple electrolytes in a salt solution significantly affects the stability of calcium-alginate gels due to low bound calcium fractions (Wang et al, Polymer. 39(13):2759-2764, June 1998, page 2759col.1-2, page 2763, conclusion). Furthermore, controlled gelation rate has been only achieved with CaCO3-GDL and CaSO4-CaCO3-GDL systems, which results in homogeneous alignate gels with defined dimensions for tissue engineering applications. Slower gelation systems generate more uniform and mechanically stronger gels than faster gelation systems, the comprehensive modulus and strength increases with alginate concentration total calcium contents, molecular weight and guluronic acid (G) contents of the alginate (Kuo et al Biomaterials 22:511-521, 2000).

Considering the state of art and the guidance provided in the specification, it is unclear how one skill in the art would use the any and all three-dimensional cross-linked systems wherein the any and all hydrophilic-polymers are cross-linked using any and all cation-releasing compounds. Fore example, it is unclear how one skill in the art would cross-link any and all hydrophylic polymers using K+ or Na+ cations alone. Similarly, it is unclear how one skill in

the art would use calcium ion to cross-link any and all hydrophilic polymers (e.g. polyacrylamide gels) The guidance provided in the instant specification is only limited to Calcium-alginate hydrogel system wherein the shrinking, swelling or maintaining of the hydrogel system is selectively controlled by varying a calcium ion concentration of a medium into which the three-dimensional cross-linked hydrogel system is introduced after the cross-linking.

The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The courts have clearly stated that: "A specification did not disclose what is well known in the art. See, e.g., Hybritech Inc. V. Monoclonal Antibodies, Inc., 802 F. 2d 1367, 1385, 231 USPQ 81, 94(Fed. Cir. 1986). However, that general off-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific material or of any of the conditions under which a process can be carried out, undue experimentation is required: there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". Genentech Inc. V. Novo Nordisk A/s, 42 USPQ2d 1005 (CAFC 1997). *In instant case without sufficient guidance to make and use any and all three-dimensional cross-linked systems wherein the any and all hydrophilic-polymers are cross-linked using any and all cation-releasing compounds is not considered routine and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.* See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claims 1-20, 22-38 and 39-47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 11, 23 and 34 are indefinite because it is unclear whether the "medium into which the hydrogel system is introduced" is different from the "medium or mixture into which the three-dimensional hydrogel cross-linking was performed".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-20, 22-38 and 39-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draget et al (Carb. Poly. 14:159-178, 1991, *ref of record*), Martisen et al (Biotech. Bioeng. 33:79-89, 1989) and further in view of Hauselmann et al (US Patent 5,658,343, *ref of record*) and Cao et al (Book of abstracts, BIOT-212, 211thACS National Meeting, New Orleans 1996, *ref of record*).

Draget et al teaches the formation of a gel consisting of mixing 15mM $CaCO_3$ with sodium alginate solution, then adding 30mM GDL, resulting in a final gel of pH 7 (see, e.g., pg 161, para. 2) only to avoid formation of acidic gels (page 163, para.3). Draget et al also teach that the sodium alginate can be substituted with alginate derived from *Marocystis pyrifera* or *Laminaria hyperbores,* thus altering the viscosity of the gel (pg 161, Table 1; pg 173); and that

the dimensions of the gel (e.g. thickness and diameter) are largely a function of the dimensions of the mold into which they form, and can thus be easily modified by one of ordinary skill in the art. Furthermore, maximum gel strength was reached when Ca2+ concentration was equivalent to the amount of guluronic acid residues and syneresis become prominent when the calcium contents exceeded this value (page 175, fig-13, page 177 para.3). Thus Draget clearly teaches that variation in calcium ion concentration results in the formation of hydrogels with distinct characteristics.

Martisen teaches that physical properties of beads strongly are dependent upon the composition sequential structure and molecular size of the polymers. The cited art teaches that beads with the highest mechanical strength, lowest shrinkage, best stability towards mono-valent cations and highest porosity were made from alginate with contents of L-guluronic acid higher than 70% and average length of G-blocks higher than 15 (page 79, abstract). In addition, the cited art teaches evaluation of stability of Ca-alginate gel beads towards Na+ ions by transferring gels beads to solutions containing different concentrations of $CaCl_2$ (0.001M-0.05M) and measuring the bead volume (shrinkage) every 24 hours for 3 days (page 81 col.1 para.1). The cited art teaches that gel strength and shrinkage is the function of $CaCl_2$ concentration and gelling time (page 84, col.1-2, fig-7 and 8). In addition the cited art teaches that high gel strength, low shrinkage, high stability towards Na+ ions and high permeability are the most advantageous factors for the immobilization of living cells (page 89, col.2).

Hauselmann et al teach the method of producing an alginate gel in vitro comprising cells that produce an extracellular matrix, for implantation in vivo (e.g., col. 1, lines 39-60). Hauselmann et al also teach that the molar ratio of calcium ions to carboxyl groups in the gel determines the amount of cross-linking of the gel, as well as the amount of swelling and thus size of the gel (e.g, col 7, lines 29-46, & Figure 6a,b).

Cao et al teach the method of making and using biodegradable calcium alginate gels with osteoblasts in vitro for implantation in vivo to generate bone growth. The osteoblasts were suspended 1% sodium alginate, then 0.2g of $CaSO_4$ was added to each ml of the admixt to

initiate gel formation. The mixture was injected in nude mice, which results in the new bone formation in the transplanted animals (see abstract)

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the teaching of Draget and Martisen by introducing cells (osteoblasts) as taught by Hauselmann and Cao to the Ca-alginate hydrogels composition. One would have been motivated to do this to utilize the gel as a scaffold for cell growth and differentiation for tissue engineering. It would have been further obvious in view Martisen to control the hydrogel shrinkage or swelling by transferring the hydrogels into the solutions that contain different concentration of calcium ions. One would also have been motivated to alter the calcium ion concentration and the ratio of calcium ions to alginate carboxyl groups in order to controlling the amount of gel swelling and shrinkage. One would have been motivate to control hydrogel shrinkage and swelling because these characteristics are highly desirable in tissues engineering for different applications. Therefore, the invention pertaining to specific ion concentrations and the molar ratios that results in hydrogel swelling and shrinking are the result effective variables, which could have been readily determined by one of ordinary skill in the art especially in view of Draget and Martisen. Thus the invention as claimed is prima facie obvious in view of cited art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor

Irem.Yucel can be reached on (703) 305-1998. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Zeta Adams, whose telephone number is (703) 305-3291.

S. Kaushal
Patent examiner

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER